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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/918,589	07/30/2001	Cale M. Halbleib	0942.7200001	2015

26191 7590 06/16/2006

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EXAMINER	
SHAFER, SHULAMITH H	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/918,589	HALBLEIB ET AL.	
	Examiner	Art Unit	
	Shulamith H. Shafer, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *08 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,19,22,24 and 30-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,19,22,24 and 30-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/5/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims

The finality of the previous office action, mailed 6 February 2006 is vacated. Prosecution is hereby reopened due to new grounds of rejection. The amendment of 8 May 2006 has been received and made of record. Claims 18, 19, 22, 24, 30-35 are pending. Claims 32 and 35 are amended and the amendments have been made of record. Claims 1-17, 20-21, 23, 25-29 have been cancelled.

The rejection of claims 20 and 25 in the previous office action (6 February 2006) are rendered moot; applicants have cancelled these claims.

New issues are set forth below. The text of those sections of Title 35 U.S. Code not included in this action can be found in the prior Office action.

Objections

Title:

The title is objected to because of misspelling or typographical error; the title recites "Processes for receptpor screening". Appropriate correction is required.

Information Disclosure Statement:

The Information Disclosure Statement received on 5 May 2006 and has been made of record. Reference AW has been considered to the extent possible; however, it has been lined through and will not be included on the face of the file, as this document is not publicly available.

New Grounds for Rejection

35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18, 19, 22, 24, 30-35 are rejected under 35 U.S.C., second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32-34 recite incomplete method steps. Claims are incomplete for omitting essential steps. While all of the technical details of a method need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is to be practiced. The minimum requirements for method steps include a contacting step, omitted in the step of Claims 32(a) and 33(a), in which the reaction of the sample with the reagents necessary for the assay is recited, a detection step in which the reaction steps are quantified or visualized, and a correlation step describing how the results of the assay allow for the determination, which is recited in Claim 34. Furthermore, there is no concluding step recited for any of the claims 32-34.

Claims 18, 19, 22, 24, 30, 31 and 35 are included in this rejection since they depend from rejected claims.

35 U.S.C. §103

Claims 18, 24, 32-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bolger et al. (1998, WO 98/05962) in view of Roeder et al. (2001, US Patent No. 6,248,520, filed 6 July 1998), Burbaum et al. (1999, US Patent No. 5,876,946), and

Kirkemo et al. (1985, US Patent No. 4,510,251) for reasons of record in previous office action of 6 February 2006 and for reasons set forth below.

The combined teachings of Bolger et al., Roeder et al. and Burbaum et al. are outlined in detail in Office action of 6 February 2006 and below. The claims of the instant invention recite a method identifying test compounds that modulate the binding of a steroid hormone receptor to a steroid hormone ligand. The independent claim of the instant invention (claim 32) recites a method of monitoring a binding interaction of a steroid hormone receptor with a fluorescently-labeled ligand in the presence of a test compound by measuring fluorescence polarization. Claim 33 recites measuring the fluorescence polarization of a mixture of a steroid hormone receptor and a fluorescently-labeled ligand; claim 34 discloses comparing the fluorescence polarization of the two mixtures.

Bolger et al teach a method for measuring competitive binding activity of molecules to steroid hormone receptors, comprising: (1) mixing a fluorescence-emitting compound that binds to the steroid hormone receptors in a solution containing the steroid hormone receptors; (2) measuring the florescence polarization of the solution; (3) incubating the solution with at least one molecule that may compete with the compound for interaction with the steroid receptors; (4) measuring the fluorescence polarization of the solution of step (3); and (5) comparing the fluorescence polarization measurements to quantify any competitive interaction (page 4, lines 13-20). Bolger also teaches a "fluormone", a shortened term for "fluorescent hormone". The reference defines fluormone as "any molecule covered by the hormone definition and emits fluorescence" (page 7, lines 14-15). This could be interpreted to encompass a hormone with a fluorescent moiety attached to it. Bolger et al does not teach a steroid hormone receptor selected from the group consisting of an androgen receptor (AR), a glucocorticoid receptor (GR) and a progesterone receptor (PR), the fluorescent label conjugated to the steroid hormone via a ligand, and a fluorescent receptor ligand selected from the group consisting of fluorescein, fluoresceinamine, DTAF, Texas Red, BODIPY dyes, Alexa dyes, tetramethylrhodamine (TMR), and conjugatable derivatives thereof.

Roeder et al ('520) teach a method of screening agents that antagonize nuclear hormone receptor functioning. Among the nuclear hormone receptors that can be used in the assay system for screening potential drugs are the progesterone receptor, androgen receptor and glucocorticoid receptor (column 12, lines 53-67, bridging column 13, lines 1-8).

Burbaum et al ('946) teach a high throughput screening assay, using compounds found in combinatorial libraries to determine active drug candidates. Inhibition or binding by the library compounds causes a change in the amount of an optically detectable label (abstract and column 3, lines 37-40). The reference teaches fluorescently-labelled ligands displaced by library compounds (Figure 1C and column 4, line 67, bridging column 5, line 1); the label can be attached to a ligand which binds to a receptor (column 8, lines 48-50). Burbaum et al also teach that fluorescent labels suitable for use in the invention are well known and include fluorescein, rhodamine and Texas Red (column 8, lines 62-65). The '946 patent further discloses that nuclear receptors, such as steroid receptors, are advantageously expressed recombinantly and employed in an embodiment of this assay (column 7, lines 11-14).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to ultilize the nuclear hormone receptors taught by Roeder et al, i.e. the progesterone, androgen or glucocorticoid receptor, in the method of measuring competitive binding activity of molecules to steroid hormone receptors taught by Bolger et al, including the fluorescently-labelled ligands disclosed by Burbaum et al in the reaction mixture. The person of ordinary skill in the art would have been motivated to make these modifications because the art teaches that steroid receptors belong to a highly conserved family of receptors, the nuclear receptor superfamily. Nuclear receptors share a common structural organization, including common functional domains. These domains include a well-conserved DNA binding domain, a less well-conserved hinge area, and the C-terminal ligand binding domain. Homologous domains present in these receptor proteins serve similar roles in each. The differences observed in the ligand binding domain results in the diversity and specificity of the hormonal response. Furthermore, Bolger et al teach that the disclosed assay is a method for

measuring competitive binding activity of molecules to steroid hormone receptors (page 4, lines 12-13) and discloses the use of a fluormone or "fluorescent hormone" in the disclosed method. One would reasonably expect success because Bolger et al teach the success of this method utilizing steroid receptors.

However, the references cited above do not teach a method for monitoring a binding interaction of a steroid hormone receptor with a test ligand wherein the steroid hormone receptor ligand includes a steroid selected from the group consisting of a 5α-androstan derivatized at one or more of the 1, 3, 6, 7, 11, 15, 17, 18, or 19 positions with a linker conjugated to a fluorescent label; a 4-androsten derivatized at one or more of the 1, 3, 6, 7, 11, 15, 17, 18, or 19 positions with a linker conjugated to a fluorescent label; 4-pregnen derivatized at one or more of the 3, 6, 7, 11, 17, 19, 20 or 21 positions with a linker conjugated to a fluorescent label; and a dexamethasone derivatized at position 21 with a linker conjugated to a fluorescent label.

Kirkemo et al. teach a method and reagents for determining ligands in biological fluids and a novel class of aminomethyl-fluorescein derivatives which may be employed as reagents in fluorescent polarization immunoassays (column 1, lines 10-15). The '251 reference teaches a pregn-4-ene-3,20-dione derivatized at the 3' position with a animomethylfluorescein derivative (column 8, example 4, compound 4).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to ultilize the nuclear hormone receptors taught by Roeder et al, in the method of measuring competitive binding activity of molecules to steroid hormone receptors taught by Bolger et al, including the fluorescently-labelled ligands disclosed by Burbaum et al. and Kirkemo et al. in the reaction mixture. The person of ordinary skill in the art would have been motivated to make these modifications because the Kirkemo et al. teach that these aminofluorescein derivative tracer compounds may be employed in fluorescence polarization assays. One would reasonably expect success because Bolger et al teach the success of this method utilizing steroid receptors.

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bolger in view of Roeder, Burbaum and Kirkemo as applied to claim 32 and further in view of Chen (2000 US Patent No. 6,054,295).

The teachings of Bolger et al and the '520, '946 and '251 patents are discussed above. None of Bolger et al., Roeder, Burbaum, or Kirkemo teach a ligand binding domain of a steroid hormone receptor fused to an N-terminal domain selected from the group consisting of glutathione-S-transferase (GST), maltose binding protein (MBP) and thioredoxin (TRX).

Chen ('295) teaches constructs expressing fusion proteins of both full length nuclear receptors fused to GST, as well as ligand binding domains of nuclear hormone receptors fused to GST (column 14, lines 6-19). The patent discloses that these fusion proteins are useful in assays to identify compounds which modulate wild-type nuclear receptor activity (column 14, lines 6-10).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to ultilize the fusion proteins of nuclear receptors fused to GST taught by the '295 reference in the method of measuring competitive binding activity of molecules to steroid hormone receptors taught by Bolger et al, including the fluorescently-labelled ligands disclosed by Burbaum et al and Kirkemo et al in the reaction mixture. The person of ordinary skill in the art would have been motivated to make these modifications because Bolger et al teach that the disclosed assay is a method for measuring competitive binding activity of molecules to steroid hormone receptors (page 4, lines 12-13) and Chen teaches that fusions constructs are useful in assays to identify compounds which modulate wild-type nuclear receptor activity. One would reasonably expect success because Bolger et al teach the success of this method utilizing steroid receptors.

Claims 22 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bolger et al. in view of Roeder et al, Burbaum et al, and Kirkemo et al. as applied to claim 32 and further in view of Tanaka et al (1997, Glia 20:23-37).

The teachings of Bolger et al. and the '520, '946 and '251 patents are discussed above. None of Bolger et al., Roeder et al., Burbaum et al., or Kirkemo et al. teach a steroid hormone receptor ligand that binds to the LBD with a K_d of less than 20 nM or a glucocorticoid receptor (GR) wherein the K_d is 0.8±0.1 nM.

Tanaka et al. teach that a functional GR receptor in microglial cells binds [^{3}H]-corticosterone with a K_d of 0.8nM (page 23, abstract). It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to ultilize glucocorticoid ligand that binds with high affinity to the steroid receptor taught by Tanaka et al. in the method of measuring competitive binding activity of molecules to steroid hormone receptors taught by Bolger et al, including the fluorescently-labelled ligands disclosed by Burbaum et al and Kirkemo et al in the reaction mixture. The person of ordinary skill in the art would have been motivated to make these modifications because Tanaka et al. teach that corticosteroids may modulate brain functions through their actions on astrocytes and oligodendrocytes because these glial cells express GR (page 24, column 1, 2nd paragraph) and a method of modulating the hormone binding to receptor would identify a number of important processes in damaged nervous tissue (page 35, column 1 last sentence, bridging column 2, 1st paragraph). One would reasonably expect success because Bolger et.al teach the success of the disclosed assay is a method for measuring competitive binding activity of molecules to steroid hormone receptors (page 4, lines 12-13).

Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bolger et al. Roeder et al, Burbaum et al and Kirkemo et al. as applied to claim 32 above and further in view of Bhakta et al (1992, Arch Biochem Biophys 292:303-310).

The teachings of Bolger et al. and the '520, '946 and '251 patents are discussed above. None of Bolger et al, Roeder et al., Burbaum et al., or Kirkemo et al. teach a progesterone receptor (PR) wherein the K_d is 2.5 nM.

Bhakta et al. teach an antisteroid molecule ZK98299 that binds with high affinity (K_d of 2.5 nM) functional PR receptor in calf uterus cytosol (page 303, abstract).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to ultilize progesterone-like ligand that binds with high affinity to the PR receptor taught by Bhakta et al. in the method of measuring competitive binding activity of molecules to steroid hormone receptors taught by Bolger et al, including the fluorescently-labelled ligands disclosed by Burbaum et al and Kirkemo et al in the reaction mixture. The person of ordinary skill in the art would have been motivated to make these modifications because Bhakta et al. teach the competitive binding between the antisteroid molecule ZK98299 and progestins (page 303, abstract) and Bolger et al teach that the disclosed assay is a method for measuring competitive binding activity of molecules to steroid hormone receptors (page 4, lines 12-13). One would reasonably expect success because Bolger et al teach the success of the disclosed assay is a method for measuring competitive binding activity of molecules to steroid hormone receptors (page 4, lines 12-13),

Conclusions

*N*o claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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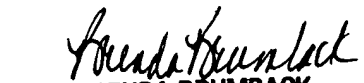

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